HCV Screening, Management, and Treatment Guidelines

Paulina Deming, PharmD, PhC
Associate Professor of Pharmacy-College of Pharmacy
Project ECHO
University of New Mexico Health Sciences Center

Brad Moran, PharmD
Chief of Pharmacy
Fort Peck Service Unit IHS

October 5, 2018
1. Recognize and stage a patient’s level of liver disease using common laboratory tests and imaging
2. Describe new therapeutic options for the treatment of chronic HCV
3. Recognize and assess the clinical significance of common drug-drug interactions with oral-HCV therapies
4. Use national algorithms and guidelines to guide treatment strategies for patients with HCV infection
Conflict of Interest Disclosure Statement
**Hepatitis**

- Spread via blood-to-blood contact
  - usually asymptomatic
- Leading cause for liver transplantation in the US
- ~75-80% of acute infections become chronic
  - chronic infection- detection of virus 6 months post-exposure
- No vaccine available
- Prevalence is 1.6% of US population
Hepatitis C is a Global Health Problem

Estimated 170 million persons with HCV infection worldwide

Prevalence of infection
- > 10%
- 2.5%-10%
- 1%-2.50%
- 1%
- NA

World Health Organization 2008 (http://www.who.int/ith/es/index.html)
Risk Factors for HCV Infection

- Persons born between 1945-1965
- Received blood transfusion or organ donation prior to 1992
- Current or former injection drug users
- Chronic hemodialysis patients
- Any known blood exposure to HCV-positive blood
- Persons with HIV
- Children born to HCV-infected mother
CDC Testing Algorithm for Chronic HCV

Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

- **HCV antibody**: Nonreactive
  - No HCV antibody detected
    - STOP*
  - Reactive
    - HCV RNA
      - Not Detected
        - No current HCV infection
          - Additional testing as appropriate†
      - Detected
        - Current HCV infection
          - Link to care
Hepatitis C Genotypes

- 6 major genotypes (1-6), most with subtypes

- Genotype 1
  - GT 1b different than GT 1a

- GT 2 easier to treat than GT 3

- GT 3 associated with higher mortality, steatohepatitis

Hepatitis C Epidemiology-Fort Peck Reservation

HCV AB TESTS PERFORMED 2010-2018
HCV Ab+ 
- 816 number of living patients

Chronic HCV 
- 562 number of living patients
- 93 *no confirmatory

Spontaneous clearance 
- 254
HCV Ab+ by age group

<table>
<thead>
<tr>
<th>Age Group</th>
<th># patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>70+</td>
<td>2</td>
</tr>
<tr>
<td>60-69</td>
<td>51</td>
</tr>
<tr>
<td>50-59</td>
<td>116</td>
</tr>
<tr>
<td>40-49</td>
<td>153</td>
</tr>
<tr>
<td>30-39</td>
<td>292</td>
</tr>
<tr>
<td>18-29</td>
<td>200</td>
</tr>
<tr>
<td>17 and younger</td>
<td>2</td>
</tr>
</tbody>
</table>
Natural history following initial infection with HCV

![Diagram showing the progression of HCV infection over time, leading to chronic hepatitis, cirrhosis, and eventually HCC or ESLD.]

- **HCV Infection**: 75-85% chance of progression to chronic hepatitis.
- **Chronic Hepatitis**: 20-30% chance of developing cirrhosis.
- **Cirrhosis**: 2-7% chance of developing HCC or ESLD per year.
HCV is Not Just a Liver Disease

Common Symptoms of HCV in Absence of Cirrhosis
• Fatigue
• Impaired cognitive function (brain fog)
• Migratory arthralgia or myalgia
• Depression

Extrahepatic Manifestations of Chronic HCV
• Renal Disease
• Lymphomas
• Neuropathy
• Dermatologic Manifestations
• Diabetes
• Neurological Impairments
Overview: Routine Evaluation and Follow Up of Persons with Chronic HCV

- Baseline studies
- Screening for other causes of liver disease
- Vaccinations
- Staging of Liver Disease
- Special considerations for cirrhotic patients:
  - Monitoring for hepatocellular carcinoma
  - Evaluation for cirrhosis related complications
  - Referral for liver transplantation
- Assessment and management of alcohol and substance abuse
Overview: Part 2- HCV Therapy

- HCV Therapies
- Special populations
- Choosing a regimen
- Common side effects and laboratory abnormalities
- Drug-drug interactions
- Monitoring of patients on HCV therapy
- Monitoring of patients after HCV therapy
Baseline Studies in Persons with Chronic HCV

- Complete blood count with differential
- Comprehensive metabolic panel including serum creatinine
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, serum albumin
- International normalized ratio (INR)
- HCV genotype and subtype
- Quantitative HCV RNA
- HIV antibody
- Hepatitis A serology (IgG or total)
- Hepatitis B serology (HBsAg, anti-HBs, anti-HBc)
- Alpha-fetal protein (AFP)
- Abdominal ultrasound with measurement of spleen size
Baseline Studies in Persons with Chronic HCV

- Complete blood count with differential
  - Identify changes consistent with cirrhosis; identify anemia especially if requiring ribavirin therapy

- Comprehensive metabolic panel including serum creatinine
  - Evaluate renal function for choosing appropriate HCV therapy

- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, serum albumin
  - Recognize level of inflammation and liver injury

- International normalized ratio (INR)
  - Assess hepatic synthetic function
Why is the CBC Important to Understand Liver Disease Severity?

- **Thrombocytopenia (<150 thousand)**
  - Due to portal hypertension caused by cirrhosis
  - Portal hypertension causes:
    - Platelets to become “stuck” in spleen
    - More platelets damaged/destroyed

- **Neutropenia**
  - Cirrhosis can cause bone marrow suppression
Abnormalities in Hepatic Panel

- Elevations in AST or ALT useful for measuring liver cell injury
  - What is normal AST or ALT? 40 IU/mL
  - Studies suggest this is too high and normal should be lower and different for men vs. women
  - **Healthy ALT** is <30 IU/mL for men and <19 IU/mL for women
- Elevations in conjugated bilirubin suggest liver disease
- Loss of liver’s ability to synthesize (lack of synthetic function) can be seen with:
  - Low serum albumin
  - Prolonged prothrombin time (elevated INR)
  - Important to look at trends in labs over time
Baseline Studies in Persons with Chronic HCV

- HCV genotype and subtype
- Quantitative HCV RNA

- HIV antibody
- Hepatitis A serology (IgG or total)
- Hepatitis B serology (HBsAg, anti-HBs, anti-HBc)

- Alpha-fetal protein (AFP)
- Abdominal ultrasound with measurement of spleen size

Determine appropriate HCV therapy and treatment duration; demonstrate chronic HCV

Share similar routes of transmission; determine need for HAV and/or HBV vaccination; determine risk for HBV reactivation

Evaluate for cirrhosis; screen for hepatocellular carcinoma
Other Viral Hepatitis

• Hepatitis A
  – Check HAV antibody (total or IgG)

• Hepatitis B
  – Check hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs; total or IgG), and hepatitis B core antibody (anti-HBc)
  – Labs needed irrespective of vaccination
# Hepatitis B Serologies

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg Anti-HBc Anti-HBs</td>
<td>Negative Negative Negative</td>
<td>Susceptible to HBV</td>
</tr>
<tr>
<td>HBsAg Anti-HBc Anti-HBs</td>
<td>Negative Positive Positive or Negative</td>
<td>Previous exposure to HBV. These patients are not immune or “protected” and frequently have subclinical infection and are at risk for reactivation with immunosuppression. There is no role to vaccinate (or boost) these patients.</td>
</tr>
<tr>
<td>HBsAg Anti-HBc Anti-HBs</td>
<td>Negative Negative Positive</td>
<td>Immune to HBV due to HBV vaccine</td>
</tr>
<tr>
<td>HBsAg Anti-HBc IgM anti-HBc Anti-HBs</td>
<td>Positive Positive Positive Negative</td>
<td>Acute HBV infection</td>
</tr>
<tr>
<td>HBsAg Anti-HBc IgM anti-HBc Anti-HBs</td>
<td>Positive Positive Negative Negative</td>
<td>Chronic HBV infection</td>
</tr>
</tbody>
</table>
HBV Reactivation Risk in HCV

- FDA warning issued 2016 following 24 reported cases of HBV reactivation in patients treated with HCV DAAs
  - 2 deaths
  - 1 liver transplant
- Mechanism of reactivation unclear
  - HCV DAAs do not have immunosuppressive effects
- Current recommendations are to “evaluate patients for potential coinfection of HCV and HBV”
Project ECHO HBV Monitoring for Patients on HCV Treatment

Check HBsAg, anti-HBc and anti-HBs

- (+) anti-HBc
- (-) HBsAg

HBsAg

- (-) Liver Panel* every 4 weeks
  - ALT ≥2x baseline OR ≥2xULN

- (+) HBsAg‡

HBVDNA quant

AND

- Start TDF or ETV

Consult viral hepatitis specialist regarding the management of HBV treatment after completing HCV DAA treatment

No additional HBV monitoring required

HBV Vaccination if anti-HBs negative

* Liver panel every 4 weeks while on HCV treatment and at 12 weeks post-treatment.

‡ HBsAg can be drawn at the same as HBVDNA for convenience or can ask for HBsAg with reflex HBVDNA.
Vaccinations

• HAV
• HBV
• Pneumococcal vaccine for all patients with chronic liver disease, including on-going alcoholism
• Annual flu
Disease States Potentiating Fibrosis

- NASH
- NAFLD
- Alcohol
- Viral Hepatitis
- HIV
- Autoimmune

Practice guidelines: [http://www.aasld.org/practiceguidelines/Pages/default.aspx](http://www.aasld.org/practiceguidelines/Pages/default.aspx)
Natural history following initial infection with HCV

Time

- 20-25 years
- 25-30 years

HCV Infection → Chronic Hepatitis (75-85%)

Chronic Hepatitis → Cirrhosis (20-30%)

Cirrhosis → HCC ESLD (2-7% per year)
Findings Suggestive of Advanced Fibrosis/ Cirrhosis

- Presence or history of ascites or esophageal varices
- Low platelet count (<150,000 mm$^3$)
- APRI $\geq$ 1.0
- FIB-4 $\geq$ 3.25
- Fibrosure $\geq$ 0.72
- Imaging with evidence of cirrhosis (nodular contour of liver or evidence of portal hypertension)
- Liver biopsy with F3 or F4 fibrosis
- Transient elastography consistent with advanced fibrosis/cirrhosis
AST to Platelet Ratio Index (APRI) Calculator

This is an AST to Platelet Ratio Index calculator tool. Enter the required values to calculate the APRI value. The APRI Score will appear in the oval on the far right (highlighted in yellow). Most laboratories use 40 IU/L as the value for the AST upper limit of normal.

Use an upper limit of normal of 40

Interpretation:
In a meta-analysis of 40 studies, investigators concluded that an APRI cutoff of 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. Similarly, an APRI cutoff of 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis.


https://www.hepatitisc.uw.edu/page/clinical-calculators/apri
Fibrosis-4 (FIB-4) Calculator

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

\[
\text{FIB-4} = \frac{\text{Age (years)}}{\text{AST Level (U/L)}} \times \frac{\text{Platelet Count (10^9/L)}}{\text{ALT (U/L)}^{0.5}}
\]

Interpretation:
Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

Sources

https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4
# Child-Pugh Classification of Cirrhosis for Drug Dosing

<table>
<thead>
<tr>
<th></th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Encephalopathy</strong></td>
<td>None</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>Absent</td>
<td>Mild-Moderate</td>
<td>Severe/Refractory</td>
</tr>
<tr>
<td><strong>Bilirubin (mg/dL)</strong></td>
<td>&lt; 2</td>
<td>2 - 3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td><strong>Albumin (g/dL)</strong></td>
<td>&gt; 3.5</td>
<td>2.8 - 3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td><strong>INR (PT Prolongation sec over control)</strong></td>
<td>&lt;1.7 (0-4)</td>
<td>1.7-2.3</td>
<td>&gt;2.3 (&gt;6)</td>
</tr>
</tbody>
</table>
# Child-Pugh Interpretation of Hepatic Function in a Patient with Cirrhosis

<table>
<thead>
<tr>
<th>C-P Score (Class)</th>
<th>Liver Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6 (A)</td>
<td>Mild Dysfunction</td>
</tr>
<tr>
<td>7-9 (B)</td>
<td>Moderate Dysfunction</td>
</tr>
<tr>
<td></td>
<td>Moderate dose reduction (~25%) for mostly hepatically metabolized</td>
</tr>
<tr>
<td>&gt; 9 (C)</td>
<td>Severe Dysfunction</td>
</tr>
<tr>
<td></td>
<td>Significant dose reduction (~50%) for mostly hepatically metabolized</td>
</tr>
</tbody>
</table>

Note: Child Pugh Score is calculated only for patients with cirrhosis.
Liver biopsy is Gold Standard but...

- Liver biopsy is not reliable gold standard
  - Sampling error leads to misinterpretation in 10-15% of cases
  - Can miss the diagnosis of cirrhosis
  - Invasive procedure with complications
  - Expensive
  - Poor patient acceptance
  - Interpretation has significant inter observer variability

Hepatocellular Carcinoma

- Incidence of HCC is estimated at 2-8% per year in patients with chronic HCV and advanced fibrosis/cirrhosis
- All patients with cirrhosis should be screened for HCC and continue with HCC surveillance every 6 months (indefinitely)
  - Abdominal ultrasound plus AFP
  - Biomarkers
  - MRI or CT for suspicious lesions or concerns for HCC
Natural History of Chronic Liver Disease

Development of complications:
- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death
Evaluating Patients with Cirrhosis: Related Complications

- Physical exam for edema, muscle wasting, encephalopathy, and/or ascites
- Endoscopy for presence of esophageal varices and need for esophageal banding/prophylaxis

- Additional info at AASLD guidelines: https://www.aasld.org/publications/practice-guidelines-0
Patients with Cirrhosis
Decompensation Shortens Survival

All patients with cirrhosis
Median survival ~ 9 years

Decompensated cirrhosis
Median survival ~ 1.6 years

Indications for Referral to Hepatologist and for Liver Transplantation

- Periodic assessment of cirrhotic patients using a validated prognostic tool such as MELD score (Model for End-Stage Liver Disease) can predict mortality and is used as indicator for liver transplantation.
- Patients with a score of 15 or higher should be considered for evaluation of liver transplant.
# MELD Calculator and Interpretation

**Model For End-Stage Liver Disease (MELD) for ages 12 and older**

The Model for End Stage Liver Disease (MELD) predicts survival for patients with advanced liver disease.

The United Network for Organ Sharing (UNOS) made a policy change regarding a revision in the MELD scoring system on January 11, 2016 that is related to transplant listing. The new MELD scores are calculated first by determining the traditional MELD score as an initial score (MELD<sub>i</sub>), if the initial MELD<sub>i</sub> scores is 12 or greater, the score is adjusted by incorporating the serum sodium value.

**MELD**

- Serum Bilirubin (mg/dL):
- INR (International Normalized Ratio):
- Serum Creatinine (mg/dL):
- Did the patient have dialysis at least twice in the past week, or received 24 hours of CVVHD within the prior week?
- Serum Sodium (mmol/L):

MELD<sub>i</sub> score less than 12 do not require Serum Sodium correction.

**MELD Score:**

---

**Interpretation:**

**3-Month Mortality Based on MELD Scores**

The estimated 3-month mortality is based on the MELD score highlighted in yellow above.

<table>
<thead>
<tr>
<th>MELD Score</th>
<th>Mortality Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>71.3% mortality</td>
</tr>
<tr>
<td>30-39</td>
<td>52.6% mortality</td>
</tr>
<tr>
<td>20-29</td>
<td>19.6% mortality</td>
</tr>
<tr>
<td>10-19</td>
<td>6.0% mortality</td>
</tr>
<tr>
<td>9 or less</td>
<td>1.9% mortality</td>
</tr>
</tbody>
</table>

[https://www.hepatitisc.uw.edu/page/clinical-calculators/meld](https://www.hepatitisc.uw.edu/page/clinical-calculators/meld)
Alcohol and On-going Substance Abuse

• No indications to withhold HCV therapy based on active alcohol or substance use

• Tobacco - can increase risk of HCC
• Marijuana - daily use associated with increased fibrosis
• Alcohol - hepatotoxic
Disease States Potentiating Fibrosis

- NASH
- NAFLD
- Alcohol
- Viral Hepatitis
- HIV
- Autoimmune

Patient should be counseled on maintaining a healthy diet and normal BMI (<25 kg/m²)
### Mental health assessment

- Patients with HCV have higher rates of depression
- Underlying depression can affect medication adherence

#### Patient Health Questionnaire (PHQ-9)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all (0)</th>
<th>Several days (1)</th>
<th>More than half the days (2)</th>
<th>Nearly every day (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Little interest or pleasure in doing things.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>b. Feeling down, depressed, or hopeless.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>c. Trouble falling/staying asleep, sleeping too much.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>d. Feeling tired or having little energy.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>e. Poor appetite or overeating.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>f. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>g. Trouble concentrating on things, such as reading the newspaper or watching TV.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>h. Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around more than usual.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>i. Thoughts that you would be better off dead or of hurting yourself in some way.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

2. If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult
When Will There Be Good News?

- Coffee and tea may be liver protective
- Statins may be hepatoprotective and may decrease the risk of HCC

Summary: Pre-Treatment Laboratories (within 60 days of start of treatment)

- CBC with differential
- Chem 7
- Liver enzymes: ALT, AST, alkaline phosphatase
- Liver function tests: albumin, total and direct bilirubin, INR
- Vitamin D 25-OH
- Urine or serum pregnancy test for women of childbearing capacity (ribavirin only)
- Alpha fetoprotein (if cirrhosis)
- HIV RNA and CD4 count (if HIV infected)

- The following labs should be current within the past 12 months*:
  - HCV-RNA Quant

- Patients must have documentation of the following labs:
  - HCV GT and subtype
  - HBsAg, anti-HBs, anti-HBc (irrespective of vaccine history)
  - HAV Ab (unless documentation of vaccination)
  - HIV Ab

*For non-cirrhotic, treatment naïve patients with genotype 1, an HCV-RNA within 6 months of starting therapy must be available for consideration of an 8 week course of treatment.
Pre-Treatment Resistance Testing

• VERY LIMITED

• Prior to using sofosbuvir/velpatasvir in patients with HCV GT3 who have cirrhosis and/or are treatment experienced
  – RAS testing for HCV GT3- looking for Y93 mutation

• All patients with HCV GT1a when considering use of elbasvir/grazoprevir require pre-treatment resistance testing for NS5A resistance associated substitutions (RASs)
Changes in HCV Therapy
Goals of HCV Therapy

- **Cure**
  - Defined as sustained virologic response (SVR)
- **Improvements in liver function**
  - Improvements in fibrosis, reversal of cirrhosis?
  - Prevent decompensation
- **Improvements in extrahepatic manifestations of HCV**
- **Prevent deaths due to liver disease complications**
- **Prevent liver cancer**
- **Reduce rates of liver cancer recurrence**
Differences in Therapy

- **Interferon Based**
  - Injectable
  - Long duration of treatment
  - High side effect profile
  - Multiple laboratory abnormalities
  - Low cure rates

- **Direct Acting Antivirals**
  - Oral
  - Short durations
  - Minimal side effects
  - Minimal laboratory abnormalities
  - High cure rates
Treatment Terminology

- Treatment naïve (TN): no prior HCV therapy
- Treatment experienced (TE): prior HCV therapy—important to clarify which prior treatment
  - Interferon
  - Direct acting antivirals only
- Sustained virologic response (SVR): cure, defined as undetectable HCV RNA at least 12 weeks after end of treatment (EOT)
  - Durable
- Relapser: patient who achieves an undetectable HCV RNA on treatment but has a detectable HCV RNA after treatment is completed
The Evolution of Highly Effective Treatment

- **1991**: Standard IFN with RBV 6 mos
- **1998**: PegIFN 12 mos
- **2001**: PegIFN RBV 12 mos
- **2011**: PegIFN/RBV/BOC or TPV 6-12 mos
- **2013**: PegIFN/RBV/SMV 24-48 wks
- **2014**: PegIFN/RBV/SOF 12-24 wks
- **2016**: LDV/SOF >90 wks
- **2017**: SOF/VEL/Vox >90 wks

**SVR (%)**

- **2013**: BOC and TPV 80+
- **2014**: SMV 89+
- **2016**: PrOD >90
- **2017**: GLE/PIB >90

**Regimens**
- **IFN 6 mos**: 6
- **IFN 12 mos**: 16
- **IFN/RBV 6 mos**: 34
- **IFN/RBV 12 mos**: 42
- **PegIFN RBV 12 mos**: 55
- **PegIFN/RBV/BOC or TPV 6-12 mos**: 70+
- **PegIFN/RBV/SMV 24-48 wks**: 80+
- **PegIFN/RBV/SOF 12-24 wks**: 89+
- **LDV/SOF >90 wks**: >90
- **PrOD >90**: >90
- **SOF/VEL/Vox >90 wks**: >90
- **GLE/PIB >90**: >90

**Duration**
- **6 mos**: 6
- **12 mos**: 16
- **24-48 wks**: 55
- **12-24 wks**: 70+
- **12-24 wks**: 89+
- **>90 wks**: >90

**Combinations**
- **IFN + RBV**: IFN 12 mos, IFN/RBV 12 mos
- **SOF + RBV**: SOF + DCV 12 wks
- **VEL + RBV**: VEL + DCV 12-16 wks
- **BOC + TPV**: BOC + PrOD >90
- **SOF + DCV**: SOF + DCV 12 wks
- **VEL + VOX**: VEL + VOX 12 wks
- **GZR + DCV**: GZR + DCV 12 wks

**Dates**
- **1998**: PegIFN
- **2001**: PegIFN RBV
- **2011**: PegIFN/RBV/BOC or TPV
- **2013**: PegIFN/RBV/SMV
- **2014**: PegIFN/RBV/SOF
- **2016**: LDV/SOF
- **2017**: SOF/VEL/Vox
- **2018**: GLE/PIB
# HCV Direct Acting Antivirals (DAAs)

<table>
<thead>
<tr>
<th>Target</th>
<th>NS3/4A: Protease Inhibitors (-previr)</th>
<th>NS5A: Replication Complex Inhibitors (-asvir)</th>
<th>NS5B: Polymerase Inhibitors (-buvir)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulled from market</td>
<td>Boceprevir Telaprevir Simeprevir</td>
<td>Ledipasvir Ombitasvir Daclatasvir Elbasvir Velpatavir</td>
<td>Nucleotide: Sofosbuvir Non-nucleoside: Dasabuvir</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir Grazoprevir Glecaprevir Voxilaprevir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV Direct Acting Antivirals (DAAs) Generic Name</td>
<td>Brand Name</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbasvir/ Grazoprevir</td>
<td>Zepatier®</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glecaprevir/Pibrentasvir</strong></td>
<td>Mavyret®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>Harvoni®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/Ombitasvir</td>
<td>Technivie®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/Ombitasvir with Dasabuvir</td>
<td>Viekira Pak®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/ Velpatasvir</td>
<td>Epclusa®</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sofosbuvir/ Velpatasvir/Voxilaprevir</strong></td>
<td>Vosevi®</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Other Therapies**

| Ribavirin                                      | Ribasphere®, RibaPak®, Copegus®, Rebetol® |

**Single Agent Therapies**

| Daclatasvir                                    | Daklinza®             |
| Sofosbuvir                                    | Sovaldi®              |
What Predicts Treatment Success or Failure?

- Patients who are treatment naïve and non-cirrhotic have very high SVR rates
- Underlying cirrhosis can decrease SVR
- Medication adherence
Overview of HCV Therapies
• Joint guidelines of the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA)

• Updated frequently - check online for most current version of guidelines

• Available at: http://www.hcvguidelines.org/
Ledipasvir/Sofosbuvir

- Combination of
  - NS5B polymerase inhibitor (Sofosbuvir);
  - NS5A inhibitor (ledipasvir)

- Administration
  - One tablet once daily with food or without food
  - Requires acidic environment for absorption

- Indicated for GT 1 and 4 for 12 weeks

Who Can Be Treated with Ledipasvir/Sofosbuvir?

- Patients without cirrhosis
- Patients with cirrhosis, including Child’s class A, B or C cirrhosis
- Restricted to patients with glomerular filtration rates greater than 30 mL/min/1.73 m²
- Approved for use in children 12 yo and older or 35 kg and above
ION Phase 3 Program (ION-1, ION-2, ION-3)

Efficacy Summary

- 97% (1886/1952) overall SVR rate

Error bars represent 95% confidence intervals.

Sofosbuvir/Velpatasvir

- Fixed-dose combination of sofosbuvir (NS5B inhibitor) and velpatasvir (NS5A inhibitor)
- Approved for chronic HCV genotypes 1, 2, 3, 4, 5, or 6 for 12 week duration of therapy

Who Can Be Treated with SOF/VEL?

- Patients without cirrhosis
- Patients with cirrhosis, including Child’s class A, B or C cirrhosis
- Restricted to patients with glomerular filtration rates greater than 30 mL/min/1.73 m²
SVR12 by Cirrhosis Status or Treatment History

Error bars represent 95% confidence intervals.
Glecaprevir/Pibrentasvir

- Combination of
  - Glecaprevir an NS3/4A protease inhibitor
  - Pibrentasvir an NS5A inhibitor

- Dosage and administration: 3 tablets once daily with food

- Indicated for 8 weeks in patients without cirrhosis; 12 weeks if cirrhotic
Glecaprevir-Pibrentasvir for 8 or 12 weeks in Non-Cirrhotic GT 1
ENDURANCE-1: Baseline Characteristics

Glecaprevir-Pibrentasvir in Treatment-Naïve Non-Cirrhotic GT 3
ENDURANCE-3 Study: Results

ION-3: SVR 12 by Treatment Duration and Regimen (ITT Analysis)

![Graph showing SVR 12 by treatment duration and regimen.]

- **GLE-PIB:** 222/233 (95%)
- **SOF + DCV:** 111/115 (97%)
- **GLE-PIB:** 149/157 (95%)

**Patients with SVR 12 (%)**

**12-Week Regimens**

- GLE-PIB
- SOF + DCV
- GLE-PIB

**8-Week Regimen**

GLE-PIB = glecaprevir-pibrentasvir; SOF = sofosbuvir; DCV = daclatasvir
ITT = Intent-to-treat

Glecaprevir-Pibrentasvir in Genotype 1-6 with Renal Disease
EXPEDITION-4: Results

SVR12 by Type of Analysis

Patients with SVR12 (%)

<table>
<thead>
<tr>
<th>Type</th>
<th>ITT</th>
<th>mITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>102/104</td>
<td>102/102</td>
</tr>
<tr>
<td>98%</td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

1 discontinuation
1 lost to follow-up

ITT, intent-to-treat analysis; mITT, modified intent-to-treat analysis

Source: Gane E, et. al, AASLD 2016. Abstract 935.
Sofosbuvir/Velpatasvir/Voxilaprevir

- Combination of
  - NS5B polymerase inhibitor (Sofosbuvir);
  - NS5A inhibitor (Velpatasvir);
  - NS3/4A protease inhibitor (Voxilaprevir)

- Administration
  - One tablet once daily with food

- Indicated for patients who previously failed DAA therapy
Who Can Be Treated with SOF/VEL/VOX?

- Patients without cirrhosis
- Patients with Child’s class A cirrhosis (compensated cirrhosis)

- Not recommended in patients with Child’s Class B or C cirrhosis
- Restricted to patients with glomerular filtration rates greater than 30 mL/min/1.73 m²
SVR12 Results Overall and by Cirrhosis Status

**Overall**
- 96% overall SVR12
- 6 relapses
  - 1 on-treatment failure
  - 2 withdrew consent
  - 1 LTFU
- 253/263

**No Cirrhosis**
- 99% SVR12
- 1 withdrew consent
- 1 LTFU
- 140/142

**Cirrhosis**
- 93% SVR12
- 6 relapses
  - 1 on-treatment failure
  - 1 withdrew consent
- 113/121

* p <0.001 for superiority compared with prespecified 85% performance goal for SOF/VEL/VOX

** Exposure was consistent with non-adherence
POLARIS-1: SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor- Experienced HCV GT 1–6

SVR12 by Genotype and Cirrhosis Status

*1/1 patient with GT unknown achieved SVR12; †4/4 patients with GT 1 other (cirrhosis, n=2; no cirrhosis, n=2) achieved SVR12; ‡Includes only GT 4 patients.

Data on file, Gilead Sciences
SVR12 by Genotype and Cirrhosis Status

**SOF/VEL/VOX 12 Weeks**
Overall SVR12 97%

**SOF/VEL 12 Weeks**
Overall SVR12 90%

Data on file, Gilead Sciences
Ribavirin

• Still utilized in combination with other HCV therapies in more difficult to treat patient populations and/or when specific RAS concerns exist

• Well-known to cause toxicity profile
  – Hemolytic anemia
    ▪ Occurs within 1-2 weeks and peaks after 4-6 weeks
    ▪ Can see increase in indirect bilirubin
  – Teratogenic
    ▪ Pregnancy category X
Side Effect Profile of DAAs

• Overall very well tolerated
• Most commonly reported side effects:
  – Headache
  – Fatigue
  – Nausea
  – Diarrhea (reported with voxilaprevir)
Laboratory Abnormalities with DAAs

• Overall not common
• Most common laboratory abnormalities:
  – ALT elevations
    ▪ Concomitant use of ethinyl-estradiol with glecaprevir/pibrentasvir
  – Bilirubin elevations
    ▪ Many DAAs inhibit bilirubin transporters
  – Anemia with concomitant use of ribavirin
    ▪ Ribavirin causes hemolytic anemia
# Rapid Viral Decline

<table>
<thead>
<tr>
<th>Actual Date</th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/26/2016</td>
<td>4.78</td>
<td>5.16</td>
<td>5.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.6</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.4</td>
<td>13.2</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38.3</td>
<td>42.7</td>
<td>44.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>93</td>
<td>73</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.83</td>
<td>0.80</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>168</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>91</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>7.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>241</td>
<td>202</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA</td>
<td>614718</td>
<td></td>
<td>&lt;15 ND</td>
<td></td>
</tr>
<tr>
<td>HCV Log</td>
<td></td>
<td></td>
<td>&lt;1.18</td>
<td></td>
</tr>
</tbody>
</table>
### Rapid Improvements in Inflammation

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Date</td>
<td>06/01/2017</td>
<td>06/08/2017</td>
<td>06/15/2017</td>
<td>06/29/2017</td>
<td>07/27/2017</td>
<td>08/24/2017</td>
<td>11/16/2017</td>
</tr>
<tr>
<td>WBC</td>
<td>5.9</td>
<td>6.8</td>
<td>6.1</td>
<td>4.8</td>
<td>5.3</td>
<td>5.6</td>
<td>7.0</td>
</tr>
<tr>
<td>ANC</td>
<td>3.5</td>
<td>2.8</td>
<td>3.4</td>
<td>2.2</td>
<td>2.6</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>HGB</td>
<td>14.1</td>
<td>13.9</td>
<td>13.3</td>
<td>14.2</td>
<td>13.8</td>
<td>14.3</td>
<td>14.2</td>
</tr>
<tr>
<td>HCT</td>
<td>43.6</td>
<td>41.0</td>
<td>40.8</td>
<td>42.8</td>
<td>41.3</td>
<td>42.5</td>
<td>43.3</td>
</tr>
<tr>
<td>Platelets</td>
<td>322</td>
<td>363</td>
<td>308</td>
<td>253</td>
<td>273</td>
<td>276</td>
<td>315</td>
</tr>
<tr>
<td>Creatinine</td>
<td>.088</td>
<td>0.89</td>
<td>0.87</td>
<td>0.82</td>
<td>0.89</td>
<td>0.82</td>
<td>0.78</td>
</tr>
<tr>
<td>AST SGOT</td>
<td>74</td>
<td>14</td>
<td>16</td>
<td>13</td>
<td>13</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>ALT SGPT</td>
<td>102</td>
<td>42</td>
<td>15</td>
<td>11</td>
<td>13</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Total Prot</td>
<td>6.7</td>
<td>6.6</td>
<td>7.1</td>
<td>6.7</td>
<td>6.4</td>
<td>7.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.9</td>
<td>3.8</td>
<td>4.2</td>
<td>4.2</td>
<td>4.0</td>
<td>4.3</td>
<td>4.2</td>
</tr>
<tr>
<td>T. Bili</td>
<td>0.3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.4</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Dir Bili</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alk Phos</td>
<td>53</td>
<td>42</td>
<td>43</td>
<td>40</td>
<td>47</td>
<td>44</td>
<td>56</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>5910</td>
<td></td>
<td></td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV Log</td>
<td>3.772</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ribavirin Induced Hemolytic Anemia

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Date</td>
<td>03/15/2018</td>
<td>03/22/2018</td>
<td>03/29/2018</td>
<td>04/12/2018</td>
<td>05/10/2018</td>
<td>06/14/2018</td>
</tr>
<tr>
<td>WBC</td>
<td>4.1</td>
<td>3.8</td>
<td>4.7</td>
<td>2.8</td>
<td>3.2</td>
<td>3.0</td>
</tr>
<tr>
<td>ANC</td>
<td>3</td>
<td>2.5</td>
<td>3.3</td>
<td>1.7</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>HGB</td>
<td>15.2</td>
<td>14.0</td>
<td>14.1</td>
<td>12.5</td>
<td>12.1</td>
<td>11.5</td>
</tr>
<tr>
<td>HCT</td>
<td>42</td>
<td>40</td>
<td>41</td>
<td>38</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Platelets</td>
<td>38</td>
<td>38</td>
<td>43</td>
<td>45</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.07</td>
<td>0.95</td>
<td>.99</td>
<td>1.00</td>
<td>0.99</td>
<td>1.02</td>
</tr>
<tr>
<td>AST SGOT</td>
<td>36</td>
<td>15</td>
<td>18</td>
<td>19</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>ALT SGPT</td>
<td>40</td>
<td>28</td>
<td>23</td>
<td>27</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Total Prot</td>
<td>7.6</td>
<td>6.7</td>
<td>6.9</td>
<td>6.5</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.1</td>
<td>4.1</td>
<td>3.8</td>
<td>3.8</td>
<td>3.7</td>
<td>3.8</td>
</tr>
<tr>
<td>T. Bili</td>
<td>1.5</td>
<td>1.0</td>
<td>1.3</td>
<td>1.3</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Dir Bili</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alk Phos</td>
<td>130</td>
<td>95</td>
<td>100</td>
<td>100</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>7720000</td>
<td></td>
<td></td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>HCV Log</td>
<td>6.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribavirin</td>
<td>1000 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What About Medications in Patients with HCV?

• In patients undergoing HCV therapy
  – Avoid herbals
  – Verify potential drug interactions using Liverpool website

• In patients with cirrhosis
  – Avoid NSAIDs
  – Acetaminophen preferred for short-term pain management at <2 grams per day
Other Main Drug Interaction Concerns for DAAs

• Statins:
  – Interactions vary by DAA and statin

• Acid suppressive therapy:
  – Ledipasvir and velpatasvir require acidity for absorption – greatest concern with velpatasvir

• Avoid amiodarone
  – Amiodarone with sofosbuvir and other DAA: Serious symptomatic bradycardia
Major Drug-Drug Interactions for all Direct Acting Antivirals

• Carbamazepine
• Oxcarbazepine
• Phenytoin
• Phenobarbital
• Rifampin

• Expected to ↓ concentrations
• DO NOT USE WITH HCV THERAPY!
HEP Drug Interaction Checker
Access our comprehensive, user-friendly, free drug interaction charts. Providing clinically useful, reliable, up-to-date, evidence-based information

Start Now

www.hep-druginteractions.org
Also available as an app: hepichart
Use of HCV Therapies in Special Populations
# Use of HCV DAAs in Renal Insufficiency and Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Ledipasvir/sofosbuvir</th>
<th>Elbasvir/grazoprevir</th>
<th>Sofosbuvir/velpatasvir</th>
<th>Sofosbuvir/velpatasvir/voxilaprevir</th>
<th>Glecaprevir/pibrentasvir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use in renal impairment or end-stage renal disease?</strong></td>
<td>&gt; 30 mL/min</td>
<td>Safe to use in all levels of renal impairment including dialysis</td>
<td>&gt; 30 mL/min</td>
<td>&gt; 30 mL/min</td>
<td>Safe to use in all levels of renal impairment including dialysis</td>
</tr>
<tr>
<td><strong>Use in cirrhosis?</strong></td>
<td>Childs Class A, B or C</td>
<td>Child Class A</td>
<td>Childs Class A, B or C</td>
<td>Child Class A</td>
<td>Child Class A</td>
</tr>
</tbody>
</table>

- **Ledipasvir/sofosbuvir**: Use in renal impairment or end-stage renal disease? > 30 mL/min. Safe to use in all levels of renal impairment including dialysis.
- **Elbasvir/grazoprevir**: Use in renal impairment or end-stage renal disease? Safe to use in all levels of renal impairment including dialysis.
- **Sofosbuvir/velpatasvir**: Use in renal impairment or end-stage renal disease? > 30 mL/min. Safe to use in all levels of renal impairment including dialysis.
- **Sofosbuvir/velpatasvir/voxilaprevir**: Use in renal impairment or end-stage renal disease? > 30 mL/min. Safe to use in all levels of renal impairment including dialysis.
- **Glecaprevir/pibrentasvir**: Use in renal impairment or end-stage renal disease? Safe to use in all levels of renal impairment including dialysis.

**Use in cirrhosis?**
- **Ledipasvir/sofosbuvir**: Childs Class A, B or C
- **Elbasvir/grazoprevir**: Child Class A
- **Sofosbuvir/velpatasvir**: Childs Class A, B or C
- **Sofosbuvir/velpatasvir/voxilaprevir**: Child Class A
- **Glecaprevir/pibrentasvir**: Child Class A
Hepatitis C: Genotype 1a Non-Cirrhotic Treatment Regimen

Is patient treatment experienced?

- **yes**
  - NS5A
    - SOF/VEL/VOX 12 weeks
      - Rating: IA
      - Or
        - G/P 12 weeks
          - Rating: Ia, B
  - SOF
    - SOF/VEL/VOX 12 weeks
      - Rating: IA
    - SOF/VEL 12 weeks
      - Rating: IA
      - Or
        - LDV/SOF 12 weeks
          - Rating: IA
          - Or
            - G/P 12 weeks
              - Rating: Ia, B
  - IFN+RBV + PI
    - SOF/VEL 12 weeks
      - Rating: IA
  - IFN + RBV
    - SOF/VEL 12 weeks
      - Rating: IA
      - Or
        - LDV/SOF 12 weeks
          - Rating: IA
          - Or
            - G/P 12 weeks
              - Rating: Ia, B

- **no**
  - SOF/VEL 12 weeks
    - Rating: IA
    - Or
      - May consider
        - LDV/SOF 8 weeks
          - Rating: IB
          - Or
            - G/P 8 weeks
              - Rating: IA

Check for NS5A RASs

- (-) RASs
  - EBR/GZR 12 weeks
    - Rating: IA

*Rating for Level of Recommendation*

These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens

Direct Acting Antivirals (DAAs):

- **EBR/GZR**: elbasvir/grazoprevir (Zepatier)
- **G/P**: glecaprevir/pibrentasvir (Mavryt)
- **LDV/SOF**: ledipasvir/sofosbuvir (Harvoni)
- **SOF/VEL**: sofosbuvir/velpatasvir (Epclusa)
- **SOF/VEL/VOX**: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)
Hepatitis C: Genotype 1b Non-Cirrhotic Treatment Regimen

Is patient treatment experienced?

yes

Which treatment?

NSSA

SOF or NSSA

IFN+RBV+PI

IFN+RBV

no

SOF/VEL/VOX 12 weeks

SOF/VEL/VOX 12 weeks

SOF/VEL 12 weeks

SOF/VEL 12 weeks

SOF/VEL 12 weeks

LDV/SOF 12 weeks

LDV/SOF 12 weeks

G/P 8 weeks

LDV/SOF 8 weeks

May consider
HCV RNA ≤ 6 million, black, not HIV

Rating: IA

Rating: IA

Rating: IA

Rating: IA

Rating: IA

Rating: IA

Rating: IA

Rating: IA

Rating: IB

Rating: IA

Rating: IA

Rating: IA

Rating: IA

Rating: IA

Direct Acting Antivirals (DAAs):
- EBR/GZR: elbasvir/grazoprevir (Zepatier)
- G/P: glecaprevir/pibrentasvir (Mavyret)
- LDV/SOF: ledipasvir/sofosbuvir (Harvoni)
- SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
- SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

*Rating for Level of Recommendation
These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens
Hepatitis C: Genotype 1b Cirrhotic Treatment Regimen

1. Does the patient have decompensated cirrhosis?
   - Yes
     - Did patient fail NS5A or SOF?
       - Yes
         - NS5A
         - SOF
           - SOF/VEL + RBV
             - 24 weeks
             - Rating: IIC
           - LDV/SOF + RBV
             - 12 weeks
       - No
         - SOF/VEL + RBV
           - 24 weeks
           - Rating: IIC
           - Or
             - SOF/VEL + RBV
               - 12 weeks
               - Rating: IA
         - If RBV Intolerant:
           - SOF/VEL
             - 24 weeks
             - Rating: IIB
           - Or
             - LDV/SOF
               - 24 weeks
               - Rating: IA
   - No
     - Is patient treatment experienced?
       - Yes
         - SOF/VEL
           - 12 weeks
           - Rating: IA
           - Or
             - LDV/SOF
               - 12 weeks
               - Rating: IA
       - No
         - G/P
           - 12 weeks
           - Rating: IIA,B
         - Or
           - SOF/VEL
             - 12 weeks
             - Rating: IIA,B
         - Or
           - EBR/GZR
             - 12 weeks
             - Rating: IA

Direct Acting Antivirals (DAAs):
- EBR/GZR: elbasvir/grazoprevir (Zepatier)
- G/P: glecaprevir/pibrentasvir (Mavyret)
- LDV/SOF: ledipasvir/sofosbuvir (Harvoni)
- RBV: ribavirin
- SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
- SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

*Rating for Level of Recommendation:
These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens.
Hepatitis C Genotype 2 Treatment Regimen Decision Tree

Genotype 2 Patients
Does the patient have cirrhosis?

yes → Is the patient decompensated?

no → Is the patient SOF experienced?

yes → Is the patient SOF experienced?

no → SOF/VEL 12 weeks
Rating: IA

SOF/VEL 12 weeks
Rating: IB

SOF DAC + RBV
Rating: IIC

If RBV Intolerant
SOF/VEL 24 weeks
Rating: IA
Or
SOF DAC 24 weeks
Rating: IIC

Direct Acting Antivirals (DAAs):
- EBR/GZR: elbasvir/grazoprevir (Zepatier)
- G/P: glecaprevir/pibrentasvir (Mavyret)
- RBV: ribavirin
- SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
- SOF DAC: sofosbuvir and daclatasvir

*Rating for Level of Recommendation
These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens
Hepatitis C Genotypes 3 Treatment Regimen Decision Tree

**Genotype 3 Patients**

Does the patient have cirrhosis?

- **yes**
  - Is the patient decompensated?
    - **yes**
      - Is the patient DAA experienced?
        - **yes**
          - SOF/VEL + RBV 24 weeks
            - Rating: IIA
          - SOF DAC + RBV 12 weeks
            - Rating: IIA
          If RBV Intolerant:
            - SOF/VEL 24 weeks
              - Rating: IIA
        - **no**
          - SOF/VEL/VOX* 12 weeks
            - Rating: IIA
            - OR
            - NSSA Testing
              - (+) Y93
                - SOF/VEL + RBV 12 weeks
                  - Rating: IIA
              - (-) Y93
                - SOF/VEL/VOX 12 weeks
                  - Rating: IIA
    - **no**
      - Is the patient treatment experienced?
        - **yes**
          - SOF/VEL/VOX* 12 weeks
            - Rating: IIA
          - SOF/VEL/VOX 12 weeks
            - Rating: IIA
          - G/P 12 weeks
            - Rating: IIA
            - OR
            - NSSA Testing
              - (+) Y93
                - SOF/VEL + RBV 12 weeks
                  - Rating: IIA
              - (-) Y93
                - SOF/VEL/VOX 12 weeks
                  - Rating: IIA
        - **no**
          - SOF/VEL 12 weeks
            - Rating: IIA

**Direct Acting Antivirals (DAAs):**

- EBR/GZR: elbasvir/grazoprevir (Zepatier)
- G/P: glecaprevir/pibrentasvir (Mavyret)
- RBV: ribavirin
- SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
- SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)
- SOF DAC: sofosbuvir and daclatasvir

*Rating for Level of Recommendation*

*IF NSSA-experienced, add weight based RBV*
# Treatment Flowsheet Example

## Hepatitis C Minimum Visit/Labs Flow Sheet

<table>
<thead>
<tr>
<th>Week of Treatment</th>
<th>Screening</th>
<th>Wk 0</th>
<th>Wk 2</th>
<th>Wk 4</th>
<th>Wk 8</th>
<th>Wk 12</th>
<th>Wk 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dates</td>
<td>N/A</td>
<td>01/01/18</td>
<td>01/15/18</td>
<td>01/29/18</td>
<td>02/26/18</td>
<td>03/26/18</td>
<td>06/18/18</td>
</tr>
</tbody>
</table>

### Visit

- Wk 0: x
- Wk 2: x
- Wk 4: x
- Wk 8: x
- Wk 12: x
- Wk 24: x

### HCV RNA

- Wk 0: x
- Wk 2: x
- Wk 4: x
- Wk 8: x
- Wk 12: x
- Wk 24: x

If HCV RNA is quantifiable, present to ECHO; re-check at week 6.

### CBC w/ Diff

- Wk 0: x
- Wk 2: x
- Wk 4: x
- Wk 8: x
- Wk 12: x
- Wk 24: x

### Chem 7

- Wk 0: x
- Wk 2: x
- Wk 4: x
- Wk 8: x
- Wk 12: x
- Wk 24: x

### LFTs/HFP

- Wk 0: x
- Wk 2: x
- Wk 4: x
- Wk 8: x
- Wk 12: x
- Wk 24: x

### HBsAg

- Wk 0: x
- Wk 2: x
- Wk 4: x
- Wk 8: x
- Wk 12: x
- Wk 24: x

### HBs Ab

- Wk 0: x
- Wk 2: x
- Wk 4: x
- Wk 8: x
- Wk 12: x
- Wk 24: x

### HBc Ab

- Wk 0: x
- Wk 2: x
- Wk 4: x
- Wk 8: x
- Wk 12: x
- Wk 24: x

### Key Points to Remember:

1. Week 0 Visit is the day of the first dose of medication.
2. Lab draws are done the end of the treatment week. Should be total or IgG.
3. HBc Ab

---

**Patient Name:**

**Date of Birth:**

**Patient ID:**

**Genotype:**
### Treatment Flowsheet Example: With Ribavirin

<table>
<thead>
<tr>
<th>Week of Treatment</th>
<th>Screening</th>
<th>Wk 0</th>
<th>Wk</th>
<th>Wk</th>
<th>Wk</th>
<th>Wk</th>
<th>Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of Tx</td>
<td></td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dates</td>
<td>N/A</td>
<td>01/01/18</td>
<td>01/15/18</td>
<td>01/29/18</td>
<td>02/26/18</td>
<td>03/26/18</td>
<td>06/18/18</td>
</tr>
<tr>
<td>Visit</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC w/ Diff</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chem 7</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFTs/HFP</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBs Ab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBe Ab*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key Points to Remember:**
1. Week 0 Visit is the day of the first dose of medication.
2. Lab draws are done at the end of each treatment week.
3. HBe Ab should be total or IgG.

**Key Points to Remember:**
- Date of Birth:
- Patient ID:
- Genotype:
Resources

• AASLD/IDSA HCV Treatment Guidelines:
  – Available at: http://www.hcvguidelines.org

• HCV Drug Interactions (University of Liverpool):
  – Available at: http://www.hep-druginteractions.org

• Educational material, clinical calculators, HCV therapy summaries (University of Washington)
  – Available at: http://www.hepatitisc.uw.edu
End of Presentation

Questions?
Poor Correlation of Ammonia Levels With Presence or Severity of Encephalopathy

Venous total ammonia $\mu$mol/L vs. Severity of Hepatic Encephalopathy

Ong et al., Am J Med 2003; 114:188
## Can Active Drug Users Adhere to HCV Therapy and Achieve Cure?

<table>
<thead>
<tr>
<th></th>
<th>Immediate Treatment Group</th>
<th>Deferred Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Drug Adherence (%)</td>
<td>SVR12, n/m</td>
</tr>
<tr>
<td>All patients</td>
<td>99.3</td>
<td>184/201 (91.5)</td>
</tr>
<tr>
<td>Patients with positive UDS at Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>99.1</td>
<td>37/44 (84.1)</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>99.9</td>
<td>9/10 (90)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>97.5</td>
<td>19/20 (95)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>99.7</td>
<td>46/51 (90.2)</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>99.7</td>
<td>56/60 (93.3)</td>
</tr>
</tbody>
</table>

n = number of all randomized patients achieving SVR12; m = number of all randomized patients with positive UDS for the indicated drug at day 1